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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/738,625	GLAZIER, ARNOLD	
	Examiner	Art Unit	
	Karen A. Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *24-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-23 and 27-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Oct 1, 2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

1. Acknowledgment is made of applicants election of Group III and the species of glutamate carboxyl peptidase. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 1-29 are pending. Claims 24-26, drawn to a non-elected inventions, is withdrawn from consideration. Claims 1-23 and 27-29 will be examined to the extent that they read on ligands for matrix metalloprotein receptors, and the specific species recited in Group III of the restriction requirement.

Claim Objections

3. Claims 1 and 2 are objected to because of the following informalities: Claim 1 lacks a grammatical conjunction between sections III and IV and claim 2 lacks a grammatical conjunction between sections V and VI. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-22 and 27-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claim 1 is vague and indefinite because the association between E and T is undefined. It is unclear if ET is restricted only to molecules having a covalent bond between E and T, or if ET encompasses molecules which are not covalently linked. For purpose of examination, both alternatives will be considered.

(B) Claim 1 recites "a group referred to as a "trigger" that can be modified in vivo, wherein said in vivo modification activated the trigger and modulates the pharmacological activity, PA". It is unclear what the pharmacological activity is in reference to. For purpose of

examination, the pharmacological activity will be read as the pharmacological activity of the effector agent, E.

(C) Claim 1 recites "and provided that T is not an antibody, or an analog of an antibody...". The outcome of said provision is missing. For purpose of examination, the claim will be read as "wherein T is not an antibody, or an analog of an antibody..."

(D) Claim 1 recites "analog of an antibody", "analog of a bispecific antibody" and "component of an antibody". The metes and bounds of an antibody "analog" and "component" are unclear. The convention usage of the word analog implies a functional similarity without structural similarity. The claim requires in part a) a tumor selective targeting ligand which selectively binds to a target receptor. Selective binding is a property of antibodies. It is unclear how an antibody "analog" can be disclaimed because an antibody analog encompasses all binding agents of non-antibody origin, which is required by part a) of the claim.

(E) Claim 1 recites "the first and the second targeting ligands" which lacks antecedent basis within the claim.

(F) Claim 2 is vague and indefinite because it is unclear if the groups I through VI are referred to in the alternative or collectively, and it is unclear how the listing of values for N1, N2, N3, N4, N5 and N6 modifies the claim, i.e. it is unclear if the values listed are independent for each "N" or if the values listed must control the values for the remaining N groups.

(G) Claim 2 recites 'N=X, or about X'. It is unclear how the term "about" modifies the integer value of X, because the metes and bounds of 'about X' is not defined either by the claim or the specification.

(H) Claim 3 recites various values for N1 through N6. It is unclear how the listing of values for N1, N2, N3, N4, N5 and N6 modifies claim 2, i.e. it is unclear if the values listed are independent for each "N" or if the values listed must control the values for the remaining N groups.

(I) Claim 4 recites various values for N1 through N6 on pages 864 through 880. It is unclear how the listing of values for N1, N2, N3, N4, N5 and N6 modifies claim 3, i.e. it is unclear if the values listed are independent for each "N" or if the values listed must control the values for the remaining N groups.

(J) It is unclear how claim 5 further modifies claim 4. Claim 5 recites the "anticancer drug of claim 4 in which the targeting ligands selectively bind to target receptors on the surface of tumor cell or in the microenvironment of the tumor cell wherein the concentration of the target receptor is greater on the surface of the tumor cell or in the microenvironment of the tumor cell than on the surface or in the microenvironment of vital normal cells". Claim 5 is ultimately dependent on claim 1 which requires in section a) that the "tumor selective targeting ligand" selectively binds to a target receptor that is increased on the surface of the tumor cell or in the microenvironment of the tumor. Thus the limitations recited in claim 5 are required for claim 1.

(K) The recitation of "compound" in claims 3 and 4 lacks antecedent basis in claims 2 and 3, respectively. For purpose of examination, the term "compound" will be read as "anticancer drug".

(L) The recitation of "biomolecule" in claim 18 lacks antecedent basis in claim 4.

(M) Claim 22 is vague and indefinite in the recitation of "an analog or derivative which bears amino acid sequence similarity to portions or a monoclonal antibody". The metes and bounds of "similarity" and "portions" are not defined, for example, with regard to percent sequence identity, or numbers of consecutive amino acid sequences, or by having the same hypervariable regions or CDR regions. It is noted that similarity to a portion of a monoclonal antibody can encompass comprising one amino acid of said monoclonal antibody.

(N) Claim 27 is vague and indefinite because the association between E1 and T1 and the association between E2 and T2 is undefined. It is unclear if ExTx is restricted only to molecules having a covalent bond between Ex and Tx, or if ExTx encompasses molecules which are not covalently linked. For purpose of examination, both alternatives will be considered.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 12 and 27-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not

described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 27 is drawn to a set of anticancer drugs referred to as E1T1 and E2T2 for co-administration to a patient wherein E1 and E2 are effector agents that exhibit synergistic toxicity to a cell, and wherein T1 comprises a targeting ligand that binds to a first target receptor and T2 comprises a second targeting ligand that binds to a second targeted receptor which is increased on a tumor cell compared to a normal cell and where the first targeting ligand binds to a targeting receptor selected from a urokinase, tissue plasminogen activator, collagenase, matrix metalloproteinase, a membrane-type matrix metalloproteinase, cathepsin B, cathepsin D, cathepsin K, cathepsin L, cathepsin O, matrilysin, matripase, plasmin, stromelysin 3, MMP1, MMP2, MMP3, MMP7, MMP9, membrane-type matrix metalloproteinase I, MMP12. Claim 28 embodies the set of compounds of claim 27 wherein the effector agent E1 inhibits the de-novo synthesis of a biomolecule that is necessary for cell replication and/or survival and the effector agent E2 inhibits a salvage pathway that an enable a cell to by-pass the metabolic block caused by E1. The art recognizes that the interaction between two drugs can produce clinical synergism which would be made up of synergism of beneficial actions and toxic effects (Fiorentino et al, Dev Oncol, 1988, Vol. 54, pp. 415-435, page 415, lines 1-8). The art recognizes combinations which are known to exert synergy with respect to toxic effect on cancer cells, such as the combination of an immunotoxin and cis-platin (the abstract of Lidor et al, Journal of Clinical Investigation, 1993, Vol. 92, pp. 2440-2447). However, the instant specification is not enabling for how to make "masked" cis-platin that will regain toxic activity only after reaction with an activated matrix metalloproteinase. Glazier (art rejection below) teaches how to make the triggers from phosphoramide mustard analogs which increase and decrease the ability of said mustard to evoke cell killing depending on the enzymatic activity contacted by the phosphoramide mustard pro-drug. However, there is no chemical similarity between the phosphoramide mustards and cis-platin and one of skill in the art would reasonable conclude that the chemical reactions used to make the phosphoramide mustard pro-drugs would not be effective for making a "masked" cis-platin prodrug because cis-platin is a co-ordination complex governed by the ability of platinum to make specific bonds. Thus the products resulting from chemical reactions performed on a phosphoramide mustard have no direct nexus with the

products resulting from the same chemical reactions on a platinum co-ordination complex such as cis-platin. Further the art recognizes that the search for combinations of drugs exerting a synergistic effect requires a great deal of empirical testing of agents known to have anti-cancer properties or that may augment an agent having anti-cancer properties (Gerson et al, WO03/070234, page 2, lines 7-15). The specification is not enabling for synergistic combinations with matrix metalloproteinases as a whole because it would not be possible to determine the synergizing drug without a "great deal of empirical testing". Therefore one of skill in the art would be subjected to undue experimentation in order to make the set of anticancer drugs of claims 27 and 28.

Claim 12 embodies the compound of claim 4 which ultimately depends on the anticancer drug of claim 1. Claim 12 requires that the effector agent is comprised of a drug that stimulates the immune system. The specification does not teach how to make an anticancer drug comprising a tumor selective targeting ligand which is not an antibody, and which consists of a targeting ligand and a trigger, wherein in vivo modification of said trigger increase the tumor killing activity and wherein in vivo modification of said trigger decreases the tumor killing activity, wherein the effector agent is a drug that stimulates the immune system

Glazier (art rejection below) teaches how to make the triggers from phosphoramide mustard analogs which increase and decrease the ability of said mustard to evoke cell killing depending on the enzymatic activity contacted by the phosphoramide mustard pro-drug . However, there is no teachings in the specification nor any art of record which would instruct one of skill in the art on how to construct the chemical trigger necessary for the regulation of cytotoxicity when the effector is an agent which stimulates the immune system. One of skill the art would be subject to undue experimentation to determine the structural attributes necessary for the appropriate "triggers" that would satisfy the requirements of claim 1. Further, one of skill in the art would be subject to further undue experimentation in order to determine how to synthesize the effectors with their appropriate triggers after determining the required structural attributes.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claim 23 is rejected under 35 U.S.C. 102(b) as being anticipated by Connors and Knox (Stem Cells, 1995, Vol. 13, pp. 501-511). Claim 23 is drawn to a compound comprising a masked intracellular transport ligand which can be modified in vivo to give an intracellular transport ligand which binds to a cell receptor that actively transport bound ligands into the cell.

Connors and Knox disclose the ADEPT system wherein carboxyl peptidase A is delivered to the exterior of a cell via and antibody followed by the administration of methotrexate-alaine which results in methotrexate after reaction with the carboxypeptidase in the vicinity of the cells (page 506, Table II, entry for carboxypeptidase A). Methotrexate binds to the folic acid receptor which actively transports bound ligands into the cell.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 1-5, 10, 13, 18, 21 and 22 are rejected under 35 U.S.C. 103(a) as being obvious over Glazier (U.S. 5,659,061) in view of Brooks et al (Cell, Feb 6, 1998, Vol. 92, pp. 391-400) and Teti et al (International Journal of Cancer, 1998 Jul 3, Vol. 77, pp. 82-93) and Fishman et al (Invasion and Metastasis, 1998, Vol. 18, pp. 15-26) and Connors and Knox (Prodrugs in Cancer Chemotherapy, Stem Cells, 1995, Vol. 13, pp. 501-511).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claim 1 is drawn to an anticancer drug ET in which E comprises one or more effector agents that evoke tumor cell killing and T comprises a) a groups which selectively binds to a target receptor that is increased on the surface of the tumor cell or in the microenvironment of a tumor cell compared to that of vital normal cells and one or more of a tumor selective targeting ligand, ii. a ligand which can be modified in vivo to give a group which binds to a tumor cell receptor that actively transport bound ligands into the tumor cell, iii. a group referred to as a "trigger" that can be modified in vivo, wherein said in vivo modification activated the trigger and modulates the pharmacological activity [of the effector agent], and iv. a ligand which binds to intracellular receptors or a ligand which can be modified in vivo to give an intracellular trapping ligand, wherein when a second targeting ligand is present in T, the first and second targeting ligands can bind simultaneously to two targeting receptor molecules, wherein when T consists of a targeting ligand and a trigger the activation of said trigger is caused by an enzyme or a catalytic activity that is increased at tumor cells or decreased at vital normal cells, wherein T is not an antibody, protein, radio labeled dimer or polymer. Claim 2 embodies the anticancer drug of claim 1 comprising N1 targeting ligands which may differ, N2 masked intracellular transport ligands which may differ, N3 triggers which may differ, N4 effector agents which may differ, N5 triggers which may differ, wherein the values for N1 through N6 are recited by the claim. Claim 3 embodies claim 2 and claim 4 embodies claim 3 wherein the values are set forth for N1 through N6. Claim 5 embodies the anticancer drug of claim 4 wherein the targeting ligands selectively bind to target receptors on the surface of tumor cell or in the microenvironment of the tumor cell wherein the concentration of the target receptor is greater on the surface of the tumor

cell or in the microenvironment of the tumor cell than on the surface or in the microenvironment of vital normal cells. It is noted that claim 5 fails to further modify claim 1 for the reasons set forth under the rejection of 112, second paragraph, above. Claim 10 embodies the anticancer drug of claim 4 wherein the effector agent is a cytotoxic drug. Claim 13 embodies the compound of claim 4 in which the effector agent comprises a group which can irreversible chemically modify one or more tumor components.

Glazier teaches anticancer drugs wherein a tumor associated protease triggers the activation and release of a phosphoramide type mustard derivative by cleaving an appropriately located amide or ester functionality, and that the mustard derivative is a potent bifunctional alkylating agent which kills tumor cells by cross linking DNA or by inactivating vital enzymes (column 2, line 65 to column 3 line 25) thus fulfilling the specific embodiments of claims 10 and 13. Glazier teaches that tumor associated proteases which activate the disclosed anticancer drugs include but are not limited to urokinase, tissue plasminogen activator, cathepsins, cathepsin B, cathepsin L, cathepsin C, Cathespsin D, plasmin, collagenase, stromilysin and dipeptidyl peptidase (column 3, lines 26-31 and claim 14). Glazier teaches that the antineoplastic drug comprises two key functionalities: a trigger which toxifies or activates the drug, and a deactivator which de-toxifies the drug, said trigger is selected such that it is activated by the tumor associated protease which is present in elevated levels in the tumor, and wherein the deactivator is selected such that it is ubiquitous to all tissues or is a spontaneous reaction independent of enzymic activity (column 3, lines 31-43), thus fulfilling the specific embodiments of claim 1. Glazier teaches the specific embodiments of the claims to the extent that the antineoplastic drugs interact with the tumor proteases of urokinase, tissue plasmininogen activator, cathepsins, cathepsin B, cathepsin L, cathepsin C, Cathespsin D, plasmin, collagenase, stromilysin and dipeptidyl peptidase which serve as "receptors" for the "targeting ligands' which are the tumor pro-drugs. Glazier teaches that the preferred embodiment for the trigger which is cleaved by the tumor proteases is Formulas 3a, 3b, 4a and 4b, wherein the preferred structure for R5 is formula 5a or 5b, wherein Rb is a substituted or unsubstituted amino acid or an oligopeptide comprised of about 2 to about 20 substituted or unsubstituted amino acids (column 5, lines 1-35). Glazier teaches preferred structures for pro-drugs comprising a de-toxification moiety (column 6, line 30 to column 7, line 27). Glazier teaches that the activated compound is

a cytotoxic phosphoramide mustard analog (column 11, lines 7-11) which is an alkylating agent and thus fulfills the specific embodiment of claim 13. Glazier does not teach targeting ligands for the receptors of matrix metalloproteinases, MMP1, 2, 3, 7, 9, 12 or 13. Glazier does not teach substrates of matrix metalloproteinases which result in the cleavage of an entire peptide from a phenol or aromatic amino group (column 9, lines 46-50) although Glazier teaches that it is within the purview of one of skill in the art to screen for oligopeptides using libraries of oligopeptides and coupling the terminal amigo acids of such peptides with a fluorescent indicator group in order to optimize the search for peptide sequences which are readily cleaved from the organic substrate to produce either a chromophore or a free cytotoxin (column 10, lines 44 to column 11, line 6).

Brooks et al (Cell, Feb 6, 1998, Vol. 92, pp. 391-400) teach that matrix metalloproteinase-2 is bound to the integrin alphavbeta3 on the surface of angiogenic blood vessels (lines 2-4 of abstract).

Teti et al (International Journal of Cancer, 1998 Jul 3, Vol. 77, pp. 82-93) teach that MMP-2 is activated by virtue of interaction with alphavbeta3 (page 88, first column, lines 3-6 under the heading "Discussion").

Fishman et al (Invasion and Metastasis, 1998, Vol. 18, pp. 15-26) teach that the interaction between type I collagen and the MMP-2 zymogen is responsible for converting the zymogen into the active enzyme and contributes to the metastatic dissemination of ovarian carcinoma cells (page 15, second column, line 21 to page 16, first column, line 12).

Connors and Knox (Prodrugs in Cancer Chemotherapy, Stem Cells, 1995, Vol. 13, pp. 501-511) teach that human tumors expresssing high levels of activated enzymes are rare (lines 11-14 of abstract).

It would have been prima facie obvious at the time the claimed invention was made to combine the MMP-2 zymogen with the R6-COOH moiety of Glazier, wherein R6 comprises an oligopeptide from about 2 to about 20 amino acids which is capable of being cleaved to render a para or ortho hydroxyl or amino group in position 5 of the aromatic ring of Formula 2(Glazier column 4) or Formula 7 (Glazier column 6) to produce a cytotoxic phosphoramide mustard analog. One of skill in the art would be motivated to do so by the teachings of Brooks et al, Teti et al and the abstract of Fishman which together teach that MMP-2 is activated by binding to

alphavbeta3 integrin which is present in angiogenic blood vessels, and the teachings of Connors and Knox on the relative rarity of human tumors which express high levels of enzymes. One of skill in the art would readily understand that a zymogen can be provided which when activated by binding to alphavbeta3 in angiogenic blood vessels or by binding to type I collagen associated with ovarian carcinoma would form the active enzyme in the vicinity of the tumor. One of skill in the art would understand that the activated enzyme can react with the pro-drug of Glazier to form the active cytotoxic agent in the vicinity of the tumor or in angiogenic blood vessels which feed a tumor.

12. Claims 1-5, 10, 11, 13, 18, 21 and 22 are rejected under 35 U.S.C. 103(a) as being obvious over Glazier (U.S. 5,659,061) and Brooks et al (Cell, Feb 6, 1998, Vol. 92, pp. 391-400) and Teti et al (International Journal of Cancer, 1998 Jul 3, Vol. 77, pp. 82-93) and Fishman et al (Invasion and Metastasis, 1998, Vol. 18, pp. 15-26) and Connors and Knox (Prodrugs in Cancer Chemotherapy, Stem Cells, 1995, Vol. 13, pp. 501-511) as applied to claims1-5, 10, 13, 18, 21 and 22 above, and in further view of Lauffer et al (WO97/36619) and Denny et al (J Pharm Pharmacol, 1998, Vol. 50, pp. 387-394) and Schlom (Monoclonal Antibodies: They're More and Less Than You Think, In: Molecular Foundations of Oncology, 1993, Broder, Ed, pages 95-133)..

Claim 11 embodies the method of claim 4 wherein the effector agent comprises a radionuclide. None of Glazier or Brooks et al or Teti et al or the abstract of Fishman et al or Connors and Knox teach a radionuclide as an effector.

Lauffer et al teach tumor targeting by means of substrates that are cleaved by matrix metalloproteinases in the vicinity of tumor cells in vivo (page 35, lines 22-33 and page 36, line 10 to page 37, line 15), wherein said cleavage results in a detectable signal via a magnetic resonance signal (claims 64-66). Lauffer et al do not teach a radiolabel as a detectable signal.

Denny et al teach a carbamate pro-drug which releases a phenol iodo-mustard which is more toxic to colon carcinoma xenografts in nude mice that the non-iodo mustard.

Schlom teaches that radio-labeled antibody conjugates need not be internalized in order to kill the tumor cell (page 108, second column, lines 11-14 under the heading "Radionuclide

mAb Conjugates"), and points to specific examples of using 131I labeled monoclonal antibodies in the clinic (page 108-109, "Radionuclide mAb Conjugates").

It would have been prima facie obvious at the time the invention was made to prepare the pro-drug to comprise a radioactive iodide. One of skill in the art would have been motivated to do so by the teachings of Lauffer et al on the utility of pro-drugs which react with matrix metalloproteinases at the site of tumors and give a detectable signal, and also by the teachings of Denny et al on the increased toxicity associated with the iodo version of the phenol mustard as well as by the teachings of Schlom who point out an advantage of using a radio-nuclide delivered to the vicinity of tumor cells in contrast to the delivery of toxin because the radioisotope can kill a cell without being internalized in said cell. Thus, one of skill in the art would understand that more toxicity would result from 131-I radio-labeled phenol iodo mustard because the compound would have two mechanisms of exerting toxicity.

13. Claims 1-5, 10, 13 and 18-22 are rejected under 35 U.S.C. 103(a) as being obvious over Glazier and Brooks et al and Teti et al and Connors and Knox as applied to claims 1-5, 10, 13, 18, 21 and 22 above, and in further view of Lauffer et al (WO 97/36619) and Liochev et al (Free Radical Biology & Medicine, 1994, Vol. 16, pp. 29-33) and Sessler et al (WO 90/10633) and Sessler et al (U.S. 5,580,543).

Claim 19 embodies the compound of claim 18 in which "V" is comprised of a chemical group that generates free radicals and wherein the generated free radicals irreversibly chemically modify the target biomolecule m. Claim 20 embodies the compound of claim 19 in which the free radical generator "V" is a non-radioactive metal-chelator complex.

Lauffer et al teach an image enhancing moiety, "IEM" comprising an iron particle or metal chelate, wherein the paramagnetic metal can be Fe(III) or Mn(III) (page 17, lines 25-34). Lauffer et al do not teach non-radioactive metal-chelator complexes which generate free radicals.

Sessler et al (WO) teach that iron and manganese are known to catalyze a variety of deleterious Fenton-type free radical reactions (page 132, lines 13-16).

Liochev et al teach that in vivo, Fe(III) is rapidly reduced to Fe(II) by cellular reductants (page 30, first column, lines 18-21). Liochev et al teach that Fe(II) reacts with hydrogen peroxide in vivo to form hydroxyl radical (page 30, second column, lines 17-22).

Sessler et al ('543) teach that the generation of hydroxyl radicals in the vicinity of the tumor causes cellular damage, thus fulfilling the embodiments of claim 19, because the reaction of hydroxyl radicals to result in cellular damage is the result of a irreversible modification of a target biomolecule.

It would have been prima facie obvious at the time the claimed invention was made to include the Fe(III) or Mn(III) metal chelates as part of the compound rendered obvious by the teachings of Glazier et al and Brooks et al and Teti et al and Connors and Knox. One of skill in the art would have been motivated to do so by the teachings of Sessler (WO) on the formation of Fenton-type products from the reaction of Fe(III) or Mn(III) which are commensurate with peroxide, hydroxide and hydrogen peroxide, as well as the teaching of Sessler et al ('543) on the induction of cellular damage by hydroxyl radicals.

14. Claims 1-9, 10, 13-18, 21, 22 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Glazier (U.S. 5,659,061) and Brooks et al (Cell, Feb 6, 1998, Vol. 92, pp. 391-400) and Teti et al (International Journal of Cancer, 1998 Jul 3, Vol. 77, pp. 82-93) and Fishman et al (Invasion and Metastasis, 1998, Vol. 18, pp. 15-26) and Connors and Knox (Prodrugs in Cancer Chemotherapy, Stem Cells, 1995, Vol. 13, pp. 501-511) as applied to claims 1-5, 10, 13, 18, 21 and 22 above and in further view of Connors and Knox (Prodrugs in Cancer Chemotherapy, Stem Cells, 1995, Vol. 13, pp. 501-511).

Claim 6 embodies the anticancer drug of claim 4 having two targeting ligands. Claim 7 embodies the anticancer drug of claim 6 wherein the targeting ligands are different and bind to different types of targeting receptors. Claims 8 and 9 embody the anticancer drug of claim 4 having three targeting ligands, and two or more targeting ligands, respectively. Claim 14 embodies the anticancer drug of claim 4 having two targeting ligands , at least one of which binds to the target receptor selected from the group consisting of a cathepsin type protease, a collagenase, matrix metalloproteinase, a membrane-type matrix metalloproteinase, cathepsin B, cathepsin D, cathepsin K, cathepsin L, cathepsin O, matrilysin, matripase, plasmin, stromelysin 3, MMP1, MMP2, MMP3, MMP7, MMP9, membrane-type matrix metalloproteinase I, MMP12. Claim 15 embodies the anticancer drug of claim 4, comprising a targeting ligand that binds the first target receptor and a second targeting ligand that binds a second target receptor listed

wherein the second targeting ligand is a collagenase, matrix metalloproteinase, a membrane-type matrix metalloproteinase, cathepsin B, cathepsin D, cathepsin K, cathepsin L, cathepsin O, matrilysin, matripase, plasmin, stromelysin 3, MMP1, MMP2, MMP3, MMP7, MMP9, membrane-type matrix metalloproteinase I, MMP12 . Claim 16 embodies the anticancer drug of claim 15 which further comprises a third targeting ligand. Claim 17 embodies the drug of claim 16 wherein the third targeting ligand binds to PSMA or glutamate carboxypeptidase II. Claim 18 embodies the anticancer drug of claim 4 in which the effector group comprises the structure RN-L-V, wherein RN binds to a target, L is a linker and V can covalently modify said target., wherein RN-L-V can bind to an irreversible modify the target. It is noted that claim 17 is vague and indefinite with respect to the terms "target biomolecule" for the reasons set forth under the rejection of 112, 2nd above.

The combination of Glazier and Brooks et al and Teti et al and the abstract of Fishman et al render obvious the specific embodiments of claims 1-5, 10, 13, 18, 21 and 22 for the reasons set forth above. Said combination does not teach the additions of a second or third effector-targeting cell ligand.

Connors and Knox teach the ADEPT system wherein carboxyl peptidase G2 is delivered to the exterior of a cell via and antibody followed by the administration of benzoic acid mustard glutamates which results in benzoic acid mustards after reaction with the carboxypeptidase in the vicinity of the cells (page 506, Table II, entry for carboxypeptidase G2) as well as the ADEPT system wherein carboxyl peptidase A is delivered to the exterior of a cell via and antibody followed by the administration of methotrexate-alaine which results in methotrexate after reaction with the carboxypeptidase in the vicinity of the cells (page 506, Table II, entry for carboxypeptidase A). Connors and Knox teach that in order to achieve a cure for most solid cancers, a hundred-fold increase in cytotoxic agents must be delivered relative to the normal clinical dose (page 501, column 2, lines 19-23).

It would have been prima facie obvious at the time the claimed invention was made to administer multiple ET combinations and combinations including carboxypeptidase II linked to an antibody. One of skill in the art would have been motivated to do so by the teachings of Connors and Knox on the specific use of antibody-targeted carboxyl peptidase G2 in activating benzoic acid mustard pro-drugs, and the further teachings of other targeted enzyme pro-drug

combinations and the need for delivering a higher dose of cytotoxic agents to a tumor in order to more effectively reduce tumor volume.

Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

An obviousness-type double-patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g. In reBerg, 140 F.3d, 1428, 46 USPQ2d 1226 (Fed. Cir. 1998): In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993): In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985).

16. Claims 1-5, 10, 13, 18, 21 and 22 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 14 of U.S. Patent No. 5,659,061 in view of Glazier (U.S. 5,659,061) in view of Brooks et al (Cell, Feb 6, 1998, Vol. 92, pp. 391-400) and Teti et al (International Journal of Cancer, 1998 Jul 3, Vol. 77, pp. 82-93) and Fishman et al (Invasion and Metastasis, 1998, Vol. 18, pp. 15-26) and Connors and Knox (Prodrugs in Cancer Chemotherapy, Stem Cells, 1995, Vol. 13, pp. 501-511).

Claim 14 of the reference patent is drawn to an antineoplatic compound which bears a masked nucleophile substituent located 3-5 atoms between the nucleophile and a leaving group, which when exposed to a tumor assoicated protease or esterase is rendered toxic to a cell, wherein the tumor assoicated protease is selected form urokinase, tpA, cathepsin B, cathepsin C, cathepsin D, plasmin, collagenase, type iv collagenase, stromelysin and dipeptidyl peptidase.

Glazier teaches anticancer drugs wherein a tumor associated protease triggers the activation and release of a phosphoramide type mustard derivative by cleaving an appropriately located amide or ester functionality, and that the mustard derivative is a potent bifunctional alkylating agent which kills tumor cells by cross linking DNA or by inactivating vital enzymes (column 2, line 65 to column 3 line 25) thus fulfilling the specific embodiments of claims 10 and 13. Glazier teaches that tumor associated proteases which activate the disclosed anticancer drugs include but are not limited to urokinase, tissue plasminogen activator, cathepsins, cathepsin B, cathepsin L, cathepsin C, Cathespsin D, plasmin, collagenase, stromilysin and dipeptidyl peptidase (column 3, lines 26-31 and claim 14). Glazier teaches that the antineoplastic drug comprises two key functionalities: a trigger which toxifies or activates the drug, and a deactivator which de-toxifies the drug, said trigger is selected such that it is activated by the tumor associated protease which is present in elevated levels in the tumor, and wherein the deactivator is selected such that it is ubiquitous to all tissues or is a spontaneous reaction independent of enzymic activity (column 3, lines 31-43), thus fulfilling the specific embodiments of claim 1. Glazier teaches the specific embodiments of the claims to the extent that the antineoplastic drugs interact with the tumor proteases of urokinase, tissue plasmininogen activator, cathepsins, cathepsin B, cathepsin L, cathepsin C, Cathespsin D, plasmin, collagenase, stromilysin and dipeptidyl peptidase which serve as "receptors" for the "targeting ligands' which are the tumor pro-drugs. Glazier teaches that the preferred embodiment for the trigger which is cleaved by the tumor proteases is Formulas 3a, 3b, 4a and 4b, wherein the preferred structure for R5 is formula 5a or 5b, wherein Rb is a substituted or unsubstituted amino acid or an oligopeptide comprised of about 2 to about 20 substituted or unsubstituted amino acids (column 5, lines 1-35). Glazier teaches preferred structures for pro-drugs comprising a de-toxification moiety (column 6, line 30 to column 7, line 27). Glazier teaches that the activated compound is a cytotoxic phosphoramide mustard analog (column 11, lines 7-11) which is an alkylating agent and thus fulfills the specific embodiment of claim 13. Glazier does not teach targeting ligands for the receptors of matrix metalloproteinases, MMP1, 2, 3, 7, 9, 12 or 13. Glazier does not teach substrates of matrix metalloproteinases which result in the cleavage of an entire peptide from a phenol or aromatic amino group (column 9, lines 46-50) although Glazier teaches that it is within the purview of one of skill in the art to screen for oligopeptides using libraries of oligopeptides

and coupling the terminal amigo acids of such peptides with a fluorescent indicator group in order to optimize the search for peptide sequences which are readily cleaved from the organic substrate to produce either a chromophore or a free cytotoxin (column 10, lines 44 to column 11, line 6).

Brooks et al (Cell, Feb 6, 1998, Vol. 92, pp. 391-400) teach that matrix metalloproteinase-2 is bound to the integrin alphavbeta3 on the surface of angiogenic blood vessels (lines 2-4 of abstract).

Teti et al (International Journal of Cancer, 1998 Jul 3, Vol. 77, pp. 82-93) teach that MMP-2 is activated by virtue of interaction with alphavbeta3 (page 88, first column, lines 3-6 under the heading "Discussion").

Fishman et al (Invasion and Metastasis, 1998, Vol. 18, pp. 15-26) teach that the interaction between type I collagen and the MMP-2 zymogen is responsible for converting the zymogen into the active enzyme and contributes to the metastatic dissemination of ovarian carcinoma cells (page 15, second column, line 21 to page 16, first column, line 12).

Connors and Knox (Prodrugs in Cancer Chemotherapy, Stem Cells, 1995, Vol. 13, pp. 501-511) teach that human tumors expresssing high levels of activated enzymes are rare (lines 11-14 of abstract).

It would have been prima facie obvious at the time the claimed invention was made to modify the antineoplastic compound of claim 14 of the reference patent by combining the MMP-2 zymogen with the R6-COOH moiety of Glazier, wherein R6 comprises an oligopeptide from about 2 to about 20 amino acids which is capable of being cleaved to render a para or ortho hydroxyl or amino group in position 5 of the aromatic ring of Formula 2(Glazier column 4) or Formula 7 (Glazier column 6) to produce a cytotoxic phosphoramide mustard analog. One of skill in the art would be motivated to do so by the teachings of Brooks et al, Teti et al and the abstract of Fishman which together teach that MMP-2 is activated by binding to alphavbeta3 integrin which is present in angiogenic blood vessels, and the teachings of Connors and Knox on the relative rarity of human tumors which express high levels of enzymes. One of skill in the art would readily understand that a zymogen can be provided which when activated by binding to alphavbeta3 in angiogenic blood vessels or by binding to type I collagen associated with ovarian carcinoma would form the active enzyme in the vicinity of the tumor. One of skill in the art

would understand that the activated enzyme can react with the pro-drug of Glazier to form the active cytotoxic agent in the vicinity of the tumor or in angiogenic blood vessels which feed a tumor.

17. All claims are rejected.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D.
5/30/2005